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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|-------------------------|------------------|
| 10/782,899 | 02/23/2004 | Minoru Fujimori | 2004_0290 | 5937 |
| 7590 04/06/2007 Thomas J. Kowalski, Esq. FROMMER LAWRENCE & HAUG LLP 745 Fifth Avenue New York, NY 10151 | | | EXAMINER LONG, SCOTT | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1633 | |
| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE | | |
| 3 MONTHS | 04/06/2007 | PAPER | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|--------------------------------------|--|--|
| Office Action Summary | Application No. 10/782,899 | Applicant(s) FUJIMORI ET AL. | |
| | Examiner Scott D. Long | Art Unit 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 February 2007.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 28-46 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 28-46 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>2/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

The examiner acknowledges receipt of amended claims, certified English translation of Japanese application (JAPAN 2000-287688) and supplemental IDS.

Response to Amendment

The amendment to claim 28 does not contain all the appropriate markings to indicate the that the amendment occurred. In the claim set of 02/06/07 in claim 28 part (2) Applicants deleted the word proliferate and inserted the phrase can replicate. This amendment is not consistent with the original claim language in claim set 9/08/2006. Claim 28 part (2) originally stated "autonomously replicates"; where did this phrase go?

The amendment was entered, but corrections should be made in any future claim amendments entered.

Claim Status

Claims 28-46 are pending. Claims 28-42 and 44-46 are amended. Claims 28-46 are under current examination.

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Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 23 February 2004 is in compliance with 37 CFR 1.63. The examiner thanks the applicant for his/her remarks regarding the mislabeling of the document listed as submitted on 28 March 2006. The mislabeled document has no bearing on the validity of the oath.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 6 February 2007 consisting of 1 sheet(s) are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a Continuation of U.S. Application No. 09/816,391 filed 26 March 2001 (abandoned). The instant application also claims benefit from foreign application JAPAN 2000-287688 filed 12 September 2000. The applicant has submitted a certified English translation of foreign application (JAPAN 2000-287688). Consequently, the application has been granted the benefit date, 12 September 2000, from foreign application JAPAN 2000-287688.

Response to Arguments - Claim Rejections 35 USC § 112

Response to Arguments – 35 USC 112, second paragraph

Applicant's arguments, see page 6 and Claim amendments, filed 6 February 2007, with respect to claims 28-46 have been fully considered and are persuasive. The rejections of Claims 28-46 under 35 USC 112, second paragraph, have been made moot by the claim amendments submitted on 6 February 2007 and are hereby withdrawn.

Response to Arguments – 35 USC 112, first paragraph (Written Description)

Applicant's arguments and amendments filed 6 February 2007, with respect to the rejection of claims 28 and 30-34, under 35 USC 112, first paragraph (Written Description) have been fully considered but they are unpersuasive.

The basis of the examiner's rejection was that there was insufficient support in the specification for claims to a large genus of promoters and terminators, because only a single example of promoter and terminator which are comprised by a Bifidobacterium Longum sequence (SEQ ID NO:1) was provided.

The applicant submitted claim amendments (specifically claim 28) which limited the promoter and terminator to any which functions in a bacterium of the genus Bifidobacterium. The examiner submits that although the scope of the newly amended claims is smaller than previously claimed, the scope of the amended claims is still much greater than the specification provides. The instant specification provides nearly verbatim language for this claim language on page 7, lines 8-9. However, there are no

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examples beyond the Bifidobacterium Longum sequences of SEQ ID NO:1 which demonstrate that the applicant is in possession of the invention commensurate with the scope of the newly amended claims.

The applicant has drawn the examiner's attention to issued patent US-6,416,754 (Brown et al), suggesting that since the issued patent presents a single working example of Clostridium acetobutylicum, yet was allowed claims to the broad genus of nonpathogenic anaerobic microorganisms, that the instant application is entitled to similarly broad claims. The examiner thanks the applicant for offering this insightful parallel. In his Remarks, the applicant also referred to the Brown et al. patent as "being related with the present invention." There does not seem to be any "relatedness" between the instant application and the Brown et al. patent, as far as DIV, CON, CIP, or other priority relationship. In response, the examiner notes that each application is examined on its own merits and the current examiner did not examine the Brown et al. application.

Therefore, the rejection of claims 28 and 30-34 under 35 USC 112, first paragraph (written description) is hereby maintained.

Response to Arguments – 35 USC 112, first paragraph (Enablement Scope)

Applicant's arguments and amendments filed 6 February 2007, with respect to the rejection of claims 28-35 and 37-41, under 35 USC 112, first paragraph (Scope of Enablement) have been fully considered and they are found persuasive.

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The applicant essentially argues that the reference by Argnani et al. which the examiner used to support a view that the state of the art of transforming *Bifidobacterium* strains was unpredictable, was in fact, an advancement in the state of the art. The applicant essentially argues that Argnani et al. developed a breakthrough technique for transforming various strains of the *Bifidobacterium* genus. The instant application utilizes the Argnani technique to transform *Bifidobacterium longum* and therefore the applicant asserts that he is enabled for transforming other *Bifidobacterium* species.

The examiner agrees with the applicants argument that Argnani et al. have developed a system "for efficient and reproducible genetic transformation of strains of the genus Bifidobacterium" (Argnani, page 109, lines 21-24) and Argnani et al. specifically mention many of the strains claimed by the applicant (claim 35).

Therefore, the rejection of claims 28 and 30-34 under 35 USC 112, first paragraph (written description) is hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 103

Applicant's arguments filed 6 February 2007 have been fully considered but they are not persuasive.

The applicant argues that the differences between Clostridium and Bifidobacterium are great enough that there would be no motivation to combine Yazawa and Brown. The applicant points out that Clostridium is associated with digestive diseases, whereas Bifidobacterium has been used to prevent diarrhea.

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The examiner notes that the target tissue of both the instant application and the inventions of Yazawa and Brown are solid tumors, not the digestive tract. The examiner also reiterates the obviousness of a combination of Yazawa and Brown. It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, namely to use a genetically modified *Bifidobacterium longum* comprising a nucleic acid sequence encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance in a method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated to introduce the DNA encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into tumor tissues under anaerobic conditions using the genetically modified bacterium because the bacterium is a nonpathogenic anaerobic bacterium, which can selectively localize to solid tumors in an individual after systemic application and pro-drug cancer therapy was well known to one of ordinary skill in the art for treating tumor tissue.

The applicant further argues that the combination of Yazawa and Brown does not teach all the limitations of claim 28, namely step 4, that the cloning vector has a selective marker that can detect specifically a bacterium belonging to the genus *Bifidobacterium* transformed with the cloning vector. The instant specification provides examples of "selective marker is used for specifically selecting the transformed bacteria of the genus *Bifidobacterium*." (page 28, lines 2-3) which include "ampicillin resistance, tetracycline resistance, neomycin resistance or kanamycin resistance; nutrition requirements" (page

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28, lines 5-7). Brown et al. specifically uses plasmids to transform the bacteria of their invention which comprise ampicillin resistance genes.

Therefore, the rejection of claims 28-46 under 35 USC 103, is hereby maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 32 is recited the phrase, "derived from Bifidobacterium Longum". What does "derived from Bifidobacterium Longum" mean? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. THIS IS A NEW MATTER REJECTION. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

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time the application was filed, had possession of the claimed invention. The instant specification does not describe promoters and terminators "derived from Bifidobacterium Longum". Could this be mutant forms of promoters? Truncated forms? There is no basis for this claim language in the instant specification as applied to promoters and terminators.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

No claims are allowed.

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Examiner Contact Information

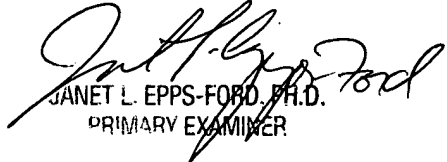
Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**.

The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott Long
Patent Examiner
Art Unit 1633


JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER